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REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the above amendments and remarks that follow. Claims 1-20 and 27-30 are pending in the application. Claims 1 and 16 have been amended to clarify that the R group is alkyl and to remove the use of the word "group" in connection with the R moiety. Claims 6, 11, and 16 have also been amended in non-limiting fashion to remove the use of the term "group" in reference to the R₅ moiety. No new matter is introduced by these amendments. Applicants respectfully submit that these amendments place the application in condition for allowance or, at the very least, place the claims in better form for appeal. For these reasons, Applicants respectfully request entry of this amendment.

I. The Claimed Invention

The present invention is directed to a polymer composition comprising a desired monofunctional polymer and a dialkoxy-terminated polymer. The dialkoxy-terminated polymer results from treating the polymer composition with an alkylating agent. As explained in the specification, this treatment step can negate the need for removal of a diol contaminant using laborious chromatography techniques. By reacting the -OH groups of the diol to form relatively inert alkoxy groups, the resulting polymer composition can be further reacted to form a highly activated monofunctional polymer reagent without also creating an activated difunctional polymer component that can lead to undesirable crosslinking when the polymer composition is reacted with a biologically active agent. Thus, as recited in Claim 1, the present invention is directed to a polymer composition comprising a mixture of a desired monofunctional polymer derivative having the structure R-O-POLY-R' and a polymer having the relatively inert structure R-O-POLY-O-R, wherein POLY is a water soluble and non peptidic polymer, such as PEG, R is alkyl, and R' is a functional group. Similarly, in Claim 16, the monofunctional polymer derivative is claimed in the absence of the polymer diol (HO-POLY-OH).

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II. §112 Claim Rejection

Claims 1-11 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner alleges that Claims 1-11 set forth an overlapping definition for R and R' because "group" is defined synonymously with "functional group" in the specification. Although Applicants respectfully submit that one of ordinary skill in the art would readily understand the difference between the claimed R and R' moieties and understand the scope of each moiety, in order to expedite prosecution, Applicants have amended Claims 1, 6, 11, and 16 in a non-limiting fashion to remove the word "group" when referring to an alkyl. It is believed that this amendment should address the Examiner's concern and further clarify that there is a clear distinction between the definition of R' and R. In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

III. §102 Claim Rejections

A. Rejection Based on U.S. Pat. No. 5,298,410

Claims 1-9 and 14-15 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,298,410 to Phillips *et al.* The Examiner specifically relies upon Examples 1-3, 6, and 7 of the Phillips reference and the disclosure appearing at column 6, line 53 through column 7, line 19. Applicants respectfully traverse this rejection.

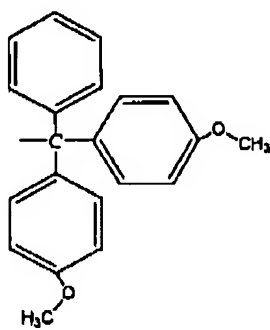
"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).


The Phillips patent is directed to the use of low diol polyalkylene glycol for covalent attachment to a biologically active proteinaceous substance, such as superoxide dismutase (SOD). The Phillips reference describes a method for removing a diol contaminant from mPEG by converting hydroxyl functionalities in the composition to dimethoxytrityl (DMT) ethers by reaction with 4,4-dimethoxytrityl chloride as described in columns 8 and 9 of the reference and in Example 4. Following conversion to DMT ethers, the composition contains mPEG-DMT contaminated with a certain amount of DMT-PEG-DMT derived from PEG-diol. The two

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components of the mixture are separated using thin layer chromatography. Once the desired mPEG-DMT product is isolated, the trityl group is cleaved from the molecule by treatment with an acid, thereby providing a purified mPEG-OH product that can be further manipulated to convert the hydroxyl group to a more reactive functional group prior to attachment to a protein, such as SOD.



DMT has the following structure: . Clearly, DMT is not an alkyl group, as recited in the present claims, since an alkyl group corresponds to any of a series of univalent groups of the general formula C_nH_{2n+1} derived from aliphatic hydrocarbons. In contrast, DMT contains unsaturated, aromatic rings, and does not fall within the well-known definition of an alkyl group as stated above.

Accordingly, a composition containing a compound having the structure DMT-PEG-DMT does not correspond to a composition containing the structure R-O-POLY-O-R, wherein R is alkyl as recited in independent Claim 1. As a result, Claim 1 and all claims dependent thereon do not lack novelty over the teachings in the Phillips reference of a composition comprising mPEG-DMT and DMT-PEG-DMT.

The sections of the Phillips reference noted in the Office Action similarly fail to anticipate Claim 1 and all claims dependent thereon. Claims 1 and 2 merely describe the functionalization of mPEG-OH by succinylation to form mPEG-S, followed by formation of the reactive ester N-succinimidyl succinate (mPEG-SS). Thereafter, the mPEG-SS is reacted with SOD to form a conjugate. Example 3 describes the preparation of pure α -hydroxy- ω -carboxymethyl PEG by preparation of partially carboxymethylated PEG followed by separation using an ionic exchange chromatography process. Example 6 simply describes preparation of mPEG-S using zero diol mPEG-OH starting material. Example 7 describes preparation of

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mPEG-SS using the mPEG-S prepared in Example 6. The portions of columns 6 and 7 of the reference listed in the Office Action merely describe the overall reaction scheme for forming a PEG conjugate of SOD using a low diol mPEG-OH starting material.

Neither these specific portions of the reference, nor any other portions of the Phillips reference, teaches the formation of a polymer mixture including a polymer having the structure R-O-POLY-O-R, wherein R is alkyl. Instead, the sections relied upon by the Examiner teach various mPEG functionalized derivatives. There is not a single compound or reagent described in the Phillips reference that has the structure R-O-POLY-O-R, where R is alkyl. It appears that the Examiner may have been relying on the possible presence of trace amounts of DMT-PEG-DMT in the mixtures described in the various examples of the Phillips reference. However, as explained above, DMT-terminated polymer molecules do not fall within the recited structure of R-O-POLY-O-R, wherein R is alkyl.

Regarding the Examiner's remarks directed towards purity of the components (page 4 of the Office action, lines 5-9), since the components/elements of the polymer composition as presently claimed and the components/elements of the polymer mixtures described in Phillips are distinctly different, the purity of the respective mixtures is immaterial to the question of novelty.

In light of foregoing, Applicants respectfully request reconsideration and withdrawal of the §102 rejection of Claim 1 and any of its dependent claims based on the Phillips reference.

B. Rejection Based on U.S. Pat. No. 5,532,150

Claims 1-9 and 14-15 also stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,532,150 to Snow *et al.* Specifically, the Examiner directs attention to Examples 1, 3-4, and 7-8 of the Snow reference as being relevant to the claimed invention. Applicants respectfully traverse this rejection.

The Snow reference is similar to the Phillips reference in suggesting the use of low diol PEG reagents for covalent attachment to SOD. As with the Phillips reference, the Snow reference suggests the formation of low diol mPEG reagents by first converting all hydroxyl functionalities to DMT ethers and separating the resulting products by reverse phase thin layer chromatography (see column 14, line 26 – column 15, lines 34). The examples mentioned in the

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Office Action are virtually identical to the five examples of the Phillips references discussed above and are irrelevant to the presently claimed invention for the same reasons outlined above in the discussion of the Phillips reference.

Thus, at most, the Snow reference teaches certain compositions that include a PEG polymer substituted with a DMT ether. However, as explained above, DMT is not an alkyl and a polymer comprising DMT ether terminal groups would not fall within the structure R-O-POLY-O-R, where R is alkyl, as claimed in independent Claim 1. Thus, the presence of DMT-PEG-DMT or mPEG-DMT in any of the compositions described in the Snow reference is immaterial to the presently claimed invention. As a result, Applicants respectfully request reconsideration and withdrawal of the §102 rejection based on the Snow reference.

IV. §103 Claim Rejections

Claims 1-9 and 14-15 also stand rejected under 35 U.S.C. §103(a) as being obvious over either the Phillips or Snow references discussed above. The Examiner opines that, since the claims are silent regarding the concentration of the polymer derivative having the structure R-O-POLY-O-R, the claims read on trace amounts. Applicants respectfully traverse these rejections and discuss these rejections together due to the substantial overlap of the teachings of the Snow and Phillips patents.

To establish a *prima facie* case of obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1975). The prior art, and not Applicant's disclosure, must provide the motivation to make the claimed combination and provide a reasonable expectation of success. *In re Vaack*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As explained above, the Phillips and Snow references fail to describe any composition comprising a polymer structure having the formula R-O-POLY-O-R, wherein R is alkyl. Since such a polymer structure is neither taught or suggested in either reference, the Examiner's comment on concentration is irrelevant to the question of patentability. Moreover, there is no suggestion to form a dialkoxy-terminated polymer in either of the cited references.

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Further, there is no motivation to modify either cited reference to arrive at a composition such as that presently claimed. For instance, there is nothing in the art to suggest modifying the Snow or Phillips references to produce a polymer terminated with alkyl groups as a replacement for the DMT groups taught therein. The DMT groups in the Snow and Phillips references are labile protecting groups that can be readily removed from the polymer terminus following removal of DMT-PEG-DMT by thin layer chromatography. There is nothing in the art of record to suggest replacement of the DMT group with any other removable protecting group, and certainly nothing to suggest replacement of DMT with an alkyl group, such as methyl. Further, there is no suggestion that an alkyl group would function in the same manner as DMT in the purification method outlined in the two cited references.

In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of the §103 rejections based on the Snow and Phillips patents.

V. Obviousness-type Double Patenting Rejections

A. Rejection Based on U.S. Pat. No. 6,362,254

Claims 1-6, 8-9, 11, 16-20, and 29-30 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-21 of U.S. Patent No. 6,362,254. The Examiner again notes that the pending claims are silent regarding the concentration of the polymer derivative having the structure R-O-POLY-O-R and, thus, read on trace amounts. Applicants respectfully traverse this rejection.

As stated in the Manual of Patent Examining Procedure (M.P.E.P.), "[o]bviousness-type double patenting requires rejection of an application claim when the claimed subject matter is **not patentably distinct** from the subject matter claimed in a commonly owned patent when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent." M.P.E.P. Section 804 (emphasis in original). See *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 58 USPQ2d 1865 (Fed. Cir. 2001); *Ex parte Davis*, 56 USPQ2d 1434, 1435-36 (Bd. Pat. App. & Inter. 2000).

Moreover, a double patenting rejection of the obviousness type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent underlying the

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double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, the analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braant*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

The '254 patent claims an activated water soluble polymer comprising a PEG polymer backbone having at least one terminus bonded to the structure $-Y-CH(X)(X')$, wherein Y is a hydrolytically stable linkage, such as oxygen, and X and X' are reactive groups containing a reactive moiety. This structure does not encompass a polymer of the type presently claimed, i.e., having the structure R-O-POLY-O-R, wherein R is alkyl. The $-CH(X)(X')$ moiety cannot correspond to an alkyl group, since the claims in the '254 patent clearly require that X and X' are reactive groups comprising a reactive moiety. Exemplary reactive moieties are listed in a number of claims of the '254 patent and include N-succinimidyl esters (e.g., Claim 7). Since alkyl groups, and alkanes in general, are extremely unreactive, an activated polymer having the structure shown above, $-CH(X)(X')$, can in no way be construed to extend to polymers having an alkyl terminus, since an alkyl group is not reactive, e.g., towards covalent attachment. Further, questions of concentration of the claimed R-O-POLY-O-R polymer are irrelevant because the claims of the '254 patent fail to suggest such a structure in even trace amounts. There is simply nothing in any of the claims of the '254 patent to suggest such a structure. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Regarding Claim 16: Independent Claim 16, and all claims dependent thereon, recite that R' of the R-O-POLY-R' polymer structure is $-O-(CH_2)_n-CHO$ or $O-(CH_2)_n-CH(ZR_5)_2$, wherein n is 1-6, Z is O or S, and R₅ is H or alkyl. The claims of the '254 patent clearly fail to teach or suggest such an R' group. The terminal structure $-Y-CH(X)(X')$ suggested in the '254 patent does not encompass such R' groups. For this additional reason, Applicants request reconsideration and withdrawal of this obviousness-type double-patenting rejection as applied to Claim 16 and any claim dependent thereon.

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B. Rejection Based on U.S. Pat. No. 6,495,659

Claims 1-8 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-21 of U.S. Patent No. 6,495,659. The Examiner again notes that the pending claims are silent regarding the concentration of the polymer derivative having the structure R-O-POLY-O-R and, thus, can be considered as reading on trace amounts of such a polymer. Applicants respectfully traverse this rejection.

The '659 patent is similarly irrelevant to Applicants' presently claimed composition. The claims of the '659 patent are directed to a sterically hindered polymer having as a terminus: $-Q-(CH_2)_m-CH(Z)-C(O)-X$, wherein Q is O or S, m is one to about 20, Z is alkyl, substituted alkyl, aryl, or substituted aryl, and X is a leaving group, such as chlorine. It appears that the Examiner is suggesting that such a terminating group would be viewed as equivalent to a polymer having a terminal group of -O-R, wherein R is alkyl. However, clearly the structure recited in the claims of the '659 patent is not equivalent to a polymer having an alkoxy group (-OR) at its terminus. Instead, the terminating group claimed in the '659 patent contains a number of heteroatoms (O or S), and an unsaturated moiety, i.e., a carbonyl group, and a leaving group. Such collection of atoms can in no way be interpreted to be equivalent to "alkyl" as recited in the present claims. As a result, such claims cannot be viewed as teaching or suggesting the structure R-O-POLY-O-R, wherein R is alkyl. The concentration of the claimed R-O-POLY-O-R polymer is utterly irrelevant because the claims of the '659 patent fail to suggest even trace amounts of such a structure. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

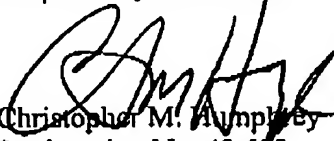
Further, contrary to the presently claimed invention, the claims of the '254 patent and the '659 patent are not expressly directed to a polymer mixture. Neither patent expressly claims a mixture of polymers and, instead, refers to only a single polymer derivative. Since each and every element of the present claims must be suggested by the claims of the '254 patent and the '659 patent to support these rejections, it is submitted that claims that fail to expressly suggest the presence of two distinct polymer species cannot be viewed as suggesting the subject matter of the pending claims. For this additional reason, Applicants request reconsideration and withdrawal of the obviousness-type double-patenting rejections.

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It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

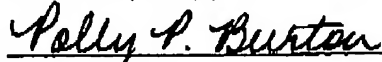
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